of mental disorder phenotypes[4,5]. Furthermore, there is initial evidence for peripheral epigenetic markers to be modifiable by psychotherapeutic interventions such as cognitive-behavioral therapy, in that disease-associated DNA methylation patterns have been shown to "normalize" along with treatment response[5]. Overall, these findings suggest a great potential for epigenetic signatures to represent: a) predictive disorder risk markers reflecting both biological and biographical vulnerability, and b) malleable targets for preventive interventions.

Indeed, in plants there is ample evidence for an epigenetic memory of resistance towards environmental pathogens, which has been proposed as a potential new direction in preventing disease in crops[6]. Also, oncological research has identified numerous epigenetic targets in cancer treatment, such as histone deacetylases (HDACs) or DNA methyltransferases (DNMTs), which could further inform preventive strategies for various diseases[7].

With respect to mental disorders, a study probing the effects of a randomized controlled family-centered prevention training program (Strong African American Families, SAAF) discerned parental depressive symptoms to be predictive of accelerated epigenetic aging in the offspring and, reciprocally, the preventive intervention to confer a protective effect regarding epigenetic aging[8].

Additionally, a lifestyle intervention such as physical activity, which is considered to contribute to the promotion of mental health, has been shown to impact the epigenetic machinery. Finally, the field of "nutritional psychiatry" has recently been refueled by evidence for folic acid and vitamin B12 to influence DNA methylation status. In turn, nutritional supplements or epigenetic modifiers such as the natural methyl-group donor S-adenosyl methionine have been suggested as promising adjuncts in the prevention of mental disorders[5].

Given this burgeoning evidence for a possible role of epigenetic processes as targetable risk markers in selective and indicated prevention of mental disorders, further research – ideally expanding to an epigenome-wide and environment-wide level as well as applying a longitudinal study design covering the critical time windows of mental disorder manifestation – is needed to validate and confirm the potential of epigenetic signatures to integratively reflect both a genetic and environmental risk, and thereby confer vulnerability to mental disorder onset.

Additionally, future studies are warranted to explore the malleability of epigenetic markers by preventive interventions. These might comprise classical preventive measures derived from cognitive-behavioral therapy, as well as explore psychopharmacological options, given that several psychoactive substances – such as selective serotonin reuptake inhibitors, antipsychotics, lithium and valproate – have already been reported to impact the epigenetic machinery. Along those lines, "epigenetic drugs" such as HDAC or DNMT inhibitors, if designed specifically enough, might catalyze preventive effects by enhancing learning and neuronal plasticity.

However, some caveats have to be considered when pursuing this line of research. While there is some evidence from studies in rodents and rhesus monkeys, or human positron emission tomography (PET) studies, for a certain comparability of peripheral and central epigenetic processes, some epigenetic signatures seem to be tissue- or even cell-specific, which might limit their use as reliable peripheral biomarkers of mental disorder risk. Also, a number of factors impacting epigenetic mechanisms – such as smoking, exercise, nutrition, body weight, alcohol and drug consumption, or physical diseases – might confound the validity of epigenetic processes as risk markers of mental disorders. Finally, as a general proviso in biomarker research, ethical guidelines and social as well as legal policies for clinical and scientific use of epigenetic information should be implemented alongside such research efforts.

In sum, epigenetics is to be considered a promising field in mental disorder prevention research. First, epigenetic markers – as accessible, integrated and dynamic biosensors of biological as well as biographical risk of mental disorders – might be particularly suited as both indicators and targets of preventive interventions. Second, epigenetic processes – if modifiable by selective or indicated preventive measures – could biologically and thus mechanistically confer resilience towards mental disorders. Finally, as epigenetically imprinted trauma has been reported to potentially be transmissible to future generations via the germline[9], successful preventive interventions embodied in epigenetic signatures might even promote a "transgenerational prevention" of mental disorders, by providing an epigenetic memory of the ability to adapt to a changing environment to future generations.

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Primary challenges and practical solutions in preventive psychiatry

Fusar-Poli et al[1] provide a scholarly and detailed overview of the state of knowledge on preventive approaches in psychiatry. Their paper should be considered an obligatory read for anyone entering or already practicing in this emerging field.

The need for preventive approaches in psychiatry is readily transparent. According to the US National Comorbidity Survey[2], a nationally representative population-based survey of mental disorders, one in two adults in the US suffers from the symptomatic and functional challenges of one mental disorder during his/her lifetime. Almost one in three adults will suffer from two or more mental disorders. Regrettably, like much else in psychiatry, preventive approaches are lagging behind general medicine. Fusar-Poli et al make strong arguments about several crucial challenges that critically hamper the implementation of preventive strategies. Here we elaborate on some of the key challenges mentioned in the review, and introduce a set of possible solutions to those.

The primary challenge is finding those who are at risk. Despite the longstanding history of neurobiological research, the underlying causal mechanisms of mental disorders remain mostly unknown. Symptom ratings have been widely used in psychiatry to detect individuals at risk. However, outside of specialty clinics, this strategy seems prone to failure. In a population-based study of 18 to 21-year-olds[3], the presence of symptoms, while associated with subsequent hospitalization for mental disorders, had positive predictive values ranging from 0.54% to 1.99%. In other words, for every correctly identified "case", there would be between 50 and 200 "non-cases" that would be *incorrectly* identified as "cases". Such a high false-positive detection rate, often found when prodrome studies are extrapolated to the general population, questions the utility of current paradigms that aim to identify at-risk groups for large-scale preventive efforts.

Advances in genetic research have identified some syndromic cases across multiple mental disorders, yet the overwhelming majority of individuals with these disorders, and especially those with common disorders (depression, anxiety), are idiopathic, with an unknown etiology. Targetable biomarkers are unavailable to use for early detection and/or efficient early intervention. As Fusar-Poli et al[1] note, only two of 162 peripheral biomarkers were reliably associated with psychosis, bipolar disorder, or depression. Collectively, our current lack of both understanding of underlying causal mechanisms and targetable biomarkers for mental disorders that can be applied at the population level substantially limit preventive strategies.

An additional challenge is that even early intervention often comes too late. Considerable evidence from genetics, epidemiology, basic neuroscience, and neuroimaging implicates early neurodevelopment as the critical period for the risk of developing most mental disorders. Almost all mental disorders are recognizable before or during the second decade of life. Yet, atypical neurobiological development surely predates the emergence of many mental disorders. For instance, evidence suggests that the first signs of cognitive abnormalities in those who will later develop schizophrenia are detectable by the age of four – decades before the disorder is usually diagnosed[4]. Furthermore, the brain most rapidly develops in utero, and continues to do so during early childhood. Indeed, evidence in children of patients with schizophrenia implicates aberrant early, possibly prenatal, brain development[5]. Therefore, these early periods are those when preventive strategies are most likely to have an impact. Fusar-Poli et al[1] highlight this point, but it is transparent that targeting this developmental period is particularly challenging.

A final challenge underscores how we address comorbidities[2]. Comorbidity rates are high in psychiatry and conform to a 50% rule. Approximately half of all people with one psychiatric disorder meet the criteria for a second disorder concurrently; half the people with two disorders meet the criteria for a third; and so on. Evidence based on multiple studies highlights a general underlying dimension, termed the p factor, which captures the tendency to develop psychopathology. In the Dunedin Multidisciplinary Health and Development Study, conducted in an unselected longitudinal birth cohort, higher scores on the general tendency to psychopathology were associated with compromised early-life brain function, and impairments in maturation[6]. Such findings foster the debate regarding categorical versus dimensional models that are relevant to research and in the clinic. In sum, since psychiatric disorders often co-occur, the challenge to clinicians is how to target higher-order psychopathological dimensions and the p factor without loss of specificity[7].

A possible way to address these challenges is to identify those cases that will contribute disproportionally to morbidity and mortality. One source of intriguing evidence comes from another study of the Dunedin Multidisciplinary Health and Development sample, showing that 80% of the health burden is attributable to 20% of cases[8]. That study showed that early-life factors (familial socioeconomic characteristics, maltreatment, IQ, and self-control) clustered into 20% of the population, that accounted for disproportionately high levels of health care use (e.g., 78% of prescription fills and 57% of hospital nights). These findings imply that early life is a critical period for preventive measures for a select group in the population. However, there is potential to abuse this approach; population segments may suffer from stigma. Nevertheless, easing the effects of childhood disadvantage is a critical aim which, if attained in early life, may support families and children, as well as benefit all of society.

A second alternative is to implement universal psychiatric prevention. General medicine has advanced in this prevention (e.g., the efficacy of the COVID-19 vaccines). Evidence-based examples in psychiatry are few, but there are some, such as means restriction to prevent suicide, and physical activity to prevent incident anxiety and depression[9]. Selective universal prevention subtly differs by stratifying prevention to a large group in the population (e.g., nutrient use among pregnant women and the elderly). Better designed, easier to administer universal prevention strategies have the potential to reduce incident mental disorders. They may involve a significant financial investment, but also indirect benefits, including improvements in general health, unemployment, and even crime.

A third alternative is to target not the outcome but an effect modifier for intervention. While biomarkers for mental disorders are not yet available, it is well established that cognitive impairment accompanies, and most often predates by many years, the onset of the majority of mental disorders. There are also reliable ways to measure cognitive functioning and plausible intervention strat-

egies. Implementing interventions to ameliorate cognitive impairments early in life may be a means for psychiatric prevention with substantial societal benefits beyond prevention of psychiatric outcomes (e.g., increasing the cognitive reserve in midlife may be a strategy to reduce dementia).

So, there are multiple challenges to implementing preventive strategies in psychiatry. There is, however, a clear need, and the time is ripe to make the leap towards primary and secondary prevention pathways in the critical period of early life and via cognition.

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Prevention in the mental health field should be implemented synergically at different levels

Fusar-Poli et al[1] present a comprehensive preventive framework for improving mental health in young people. Prevention in psychiatry is not a high funding priority, which is also reflected in the relatively low number of publications in the field. The responsibility for primary prevention and mental health promotion is placed in the social and educational sectors and, most often, the evidence base for initiatives is lacking.

In spite of research showing that risk of mental illness is associated with adversities during pregnancy and birth, low socioeconomic status, poor parenting skills, lack of stimulation and support during childhood, bullying, trauma, and early exposure to alcohol and drugs, initiatives to reduce these risk factors have attracted little scientific attention. Much can be done to improve the evidence base for early and broad preventive efforts.

Prevention of psychiatric disorders requires a coherent and multifaceted strategy, including at least five levels. The first is universal primary prevention to improve well-being (e.g., initiatives at the population level focusing on a healthy childhood, such as efforts to improve mental health literacy and parenting in early childhood). The second is universal primary prevention to prevent development of mental illness (e.g., interventions such as prevention of preterm birth and perinatal depression as well as initiatives to prevent bullying and traumatic childhood experiences and to reduce risk of adolescents engaging in substance abuse). The third is selective primary prevention to reduce risk of mental illness in risk groups (e.g., children born to parents with mental illness). The fourth is indicated primary prevention for young people showing signs or symptoms foreshadowing emerging disorder (e.g., clinical high-risk groups for psychosis or children with common mental health problems). The fifth is secondary prevention in early stages of psychiatric disorders (e.g., early intervention services in psychosis or early treatment of attention-deficit/hyperactivity disorder and autism spectrum disorders in child and adolescent services).

Here we focus briefly on selective interventions for families with parental mental illness and on indicated primary prevention initiatives, on the basis of the experience in Denmark.

Children born to parents with mental illnesses constitute an important risk group with a large prevention potential. Danish register-based figures indicate that every sixth child has a parent who has been diagnosed and treated in the secondary mental health sector. The true number at risk is likely to be even higher, since this does not include treatment in primary health care, nor those who, due to lack of accessible treatment offers, fail to be helped by health services. So, this is a very large number of children, who have been shown repeatedly to have a markedly increased risk of being diagnosed with a mental disorder before age 18[2,3], are more likely to live with a single parent[4], are at higher risk of having poor school performance[5], and have more neurocognitive, social and motor problems[6,7] than controls. Due to the parental mental illness, they are also more likely to experience insufficient support and stimulation in the home environment and to be exposed to traumatic life events – all factors that hamper their healthy developmental course.

Parental mental illness is often silenced in the family, passing on stigmatization across generations. Programmes directed towards the whole family should be developed and tested in order to change this trajectory that has been known for decades. Parental training and support as part of the recovery approach, collaboration of adult and child psychiatry with the primary sector, systematic family-based psychoeducation, and social, financial and practical support may be some elements potentially improving the functioning of the entire family and building resilience in the children at risk.

Concerning indicated prevention, implementation of transdiagnostic interventions are suggested to meet the needs of youths with common and multiple mental health problems. A Danish effectiveness study[8] documented the superiority of a new scalable transdiagnostic cognitive behavioral therapy (CBT), called "Mind My Mind" (MMM), compared to management as usual (MAU), for youths aged 6-16 years with emotional and/or behav-